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10/661,428	09/11/2003	Lars-Erik Peters	1995/US/2	8089

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EXAMINER	
WOOLWINE, SAMUEL C	
ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,428	PETERS, LARS-ERIK	
	Examiner	Art Unit	
	SAMUEL WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-35,43-47 and 49-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-35,43-47 and 49-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status

Applicant's response filed 05/07/2009 is acknowledged. Claims 22-35, 43-47, 49-65 are pending (claims 49-65 are new).

All rejections over claims 15-21 are moot as these claims have been cancelled.

The rejection of claims 22-34 and 43-47 under 35 USC 103 over Asada (WO 00/14218) in view of Qiagen News (1999) as evidenced by Uemori (US 6,673,578, providing an English translation of Asada) is maintained for the reasons of record and reiterated below. The rejection is also applied to new claims 49-61 and 63-65.

The rejection of claim 35 over Asada, Qiagen News, Uemori and Tonoike (US 6,472,187) is maintained and applied to new claim 62.

Applicant's remarks will be addressed following the reiteration of the previous rejections.

New rejections under 35 USC 112, 2nd paragraph are set forth below as necessitated by amendment.

Previous Rejections

Claim Rejections - 35 USC § 103

Claims 22-34, 43-47, 49-61 and 63-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Asada et al (WO 00/14218, the March 16, 2000 publication of international application PCT/JP99/04815) as evidenced by Uemori et al (USPN 6,673,578) and in view of Qiagen News (Issue No. 1, 1999, cover and pages 13-14). As the Asada reference was published in Japanese, USPN 6,673,578, which resulted

from the national phase entry of PCT/JP99/04815 under 35 U.S.C. 371, will be used as an English translation, and all teachings will be pointed out with reference to the '578 patent.

With regard to claims 22 and 49, Asada teaches a kit (column 12, line 33) comprising a thermostable polymerase (column 12, lines 40-45 and line 58; "Taq" is Thermus aquaticus DNA polymerase, which is thermostable), a non-nucleic acid polyanion ("acidic substance": column 13, lines 10-19 and column 9, lines 34-63; for example polyvinyl sulfates, polystyrene sulfates (column 9, line 38), sulfated-fucose-containing polysaccharides, dextran sulfate (column 9, lines 46-47)), and an appropriate polymerase reaction buffer (column 13, lines 31-34).

With regard to claims 23-25 and 50-52, Asada teaches optimization of the molecular weight of the polyanionic substances ("acidic substances"; column 10, lines 32-38).

With regard to claims 26 and 53, Asada teaches polyvinyl sulfate and polystyrene sulfate (column 9, lines 35-40).

With regard to claims 27-29 and 54-56, Asada teaches dextran sulfate, heparin, heparan sulfate, chondroitin sulfate (column 9, lines 45-50).

With regard to claims 30, 31, 57 and 58, Asada teaches optimizing the amount of the polyanionic (acidic) substance added (column 10, lines 29-33). The goal of Asada, like that of Applicant, was to add these polyanionic compounds to polymerase reactions, yet allow the polymerase to work at elevated temperature (i.e. PCR). Therefore, Asada's suggestion to optimize amounts of the polyanionic ("acidic") compounds is

compatible with the claimed amounts (which presumably allow the polymerase to function at the elevated temperatures of PCR). As set forth in MPEP 2144.05(II)(A):

"Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)"

With regard to claims 32 and 59, Asada teaches DNA polymerase ("Polymerase A", column 20, line 62; polymerase A is TaKaRa EX Taq DNA polymerase, see column 15, lines 41-49). Asada also teaches several other thermostable DNA polymerases (paragraph bridging columns 7-8).

With regard to claims 33, 34, 44, 60, 61 and 64 Taq is derived from Thermus aquaticus, which is a thermophilic Eubacteria. Asada also teaches several other thermostable DNA polymerases (paragraph bridging columns 7-8).

With regard to claims 43 and 63, "optional" limitations (in this case, a separate container comprising a reaction buffer comprising monovalent cations between about 35-100 mM) are given no patentable weight. Nevertheless, Asada teaches exemplary conditions suitable for Taq polymerase comprising 50mM potassium chloride (potassium is a monovalent cation; see column 4, lines 30-35).

With regard to claims 45 and 65, Asada teaches dextran sulfate (column 9, lines 43-47).

With regard to claim 46, Asada teaches nucleotide 5'-triphosphates (column 13, line 32).

With regard to claim 47, Asada teaches primers (column 2, lines 48-54 and column 13, lines 50-53, for example).

Asada does not teach a "pre-inhibited thermostable polymerase", wherein the thermostable polymerase is reversibly bound to the non-nucleic acid polyanion in a storage buffer, as recited in claims 22 and 49. Nor does he expressly teach storing primers in a separate container. However, the only difference between what Asada teaches and the claimed invention is the storage of the polymerase and the polyanionic substance (i.e. one of the "acidic substances" of Asada's disclosure) in one container, without primers and/or template. However, this cannot be considered a non-obvious difference because Asada explicitly teaches:

> "The above DNA polymerase, the acidic substance and other reagents may be contained in the kit in a state where each is present as an independent component, or a state in which some of the components are combined, including, for instance, a state in which the components are added to the reaction buffer and the like." (column 13, lines 34-39)

Furthermore, motivation to combine all components except primer and template into one reagent can be found in Qiagen News (Issue No. 1, 1999, cover and pages 13-14). This bulletin describes a product called HotStarTaq™ Master Mix Kit, which combines all of the components required for PCR amplification into one reagent:

> "HotStarTaq Master Mix is a ready-to-use mixture of HotStarTaq DNA Polymerase, QIAGEN PCR Buffer, and nucleotides. Setting up amplification reactions is fast and easy—simply pipet 25 µl of HotStarTaq Master Mix into each PCR tube and add 25 µl of your primers and template DNA in the PCR-quality water provided with the kit (Figure 2). The HotStarTaq Master Mix Kit provides easy handling with less pipetting, reducing the possibility of errors and contamination."

Note the mix also contains the magnesium required for the PCR reaction (see footnote to "Product" table, page 14).

It would have been *prima facie* obvious to one of ordinary skill in the art to combine the polymerase and polyanionic substance (acidic substance) taught by Asada into one container (producing a "storage buffer"), since Asada already suggested combining "some of the components" and since the Qiagen News article teaches the advantages of easy handling, less pipetting, and reduced possibility of errors and contamination. It would have been obvious to "pre-inhibit" the polymerase with the acidic substance, since Asada teaches that the addition of the acidic substance enhances the DNA synthesis reaction by "holding the DNA polymerase on its molecule, thereby suppressing the non-specific interaction of the DNA polymerase to a template DNA, and of providing an optimal amount of the DNA polymerase for the template. In other words, the DNA synthesis reaction efficiently progresses by optimizing the interaction between the template DNA and the DNA polymerase, the interaction increasing with the progress of the DNA synthesis reaction" (column 10, lines 32-38, emphasis provided). This language implies that acidic substance was initially supposed to be inhibit (hold, suppress) the polymerase.

Furthermore, in the context of a kit, one would have been motivated *not* to put the primers into the same container as the polymerase and polyanionic substance. Keeping the polymerase reagent free of any primers would allow the use of the polymerase reagent to be used in reactions for different nucleic acids targets. On the

contrary, if one made the kit with the primers already added to the polymerase reagent, then one would have been limited to reactions with only those primers.

Response to Arguments

Applicant's arguments filed 05/07/2009 have been fully considered but they are not persuasive. Applicant's main argument is in disputing the examiner's interpretation of the Asada reference as to Asada's purpose. Specifically, the examiner contends that Asada's purpose for the "acidic substance" was to reversibly inhibit the polymerase, whereas Applicant contends that Asada's purpose was to enhance DNA-synthesizing activity (section A(i) beginning on page 9 of the response).

While it is true that Asada teaches the "acidic substance" enhances DNA-synthesizing activity in a reaction (e.g. column 9, lines 34-35 of the Uemori document), this is not inconsistent with a reversible inhibition of the polymerase by the acidic substance. In the *Response to Arguments* section of the Office action mailed 01/07/2009, a comparison was presented between Applicant's disclosure and the disclosure of Asada (Uemori):

> Applicant's specification paragraph [0017]: "The present invention uses for the first time strong polyanionic polymerase inhibitors to control the activity of thermostable DNA polymerases dependent on the applied incubation temperature."
>
> Asada's disclosure column 13, lines 14-18: "The acidic substance or the salt thereof as mentioned above efficiently allows to exhibit the DNA polymerase activity or to hold the enzyme, whereby the interaction between the DNA and the enzyme can be properly regulated."
>
> Asada's disclosure column 10, lines 32-38: "The action of the acidic substance is not particularly limited, and it is considered to be on the bases of holding the DNA polymerase on its molecule, thereby suppressing the non-specific interaction of the DNA polymerase to a template DNA…"
>
> Asada's disclosure, column 9, lines 7-13: "…excess DNA polymerase is trapped with the acidic substance during the DNA synthesis reaction…".

Of the three passages from Asada (Uemori) cited above, Applicant addresses only the first two in disputing the examiner's interpretation of the purpose of the acidic substance. In fact, nowhere in the response does Applicant address Asada's teaching of "trapping" excess DNA polymerase. It is asserted that there is no other logical interpretation of the purpose of the acidic substance other than as a reversible inhibitor of the polymerase in view of the last cited passage, which in its entirety reads (column 9, lines 7-13):

> When an effective amount of the DNA polymerase for carrying out the rapid PCR of the present invention is used, since excess DNA polymerase is trapped with the acidic substance during the DNA synthesis reaction, the high-performance rapid PCR can be further achieved by supplying the most appropriate DNA polymerase for PCR to a template DNA by the effects of the acidic substance.

Hence, the acidic substance enhances the PCR reaction by trapping excess DNA polymerase during the reaction.

Applicant also interprets Asada's (Uemori's) phrase "holding the DNA polymerase on its molecule" at column 10, lines 32-38 to mean "holding the DNA polymerase onto the DNA template molecule to be replicated", and thereby enhances polymerization (last paragraph, page 10 of the response).

It is respectfully submitted, however, that this interpretation is not consistent with the statement at column 9, lines 7-13, cited above, which clearly indicates that the overall PCR reaction is enhanced by trapping excess DNA polymerase. Hence, in the

phrase "holding the DNA polymerase on its molecule", the words "its molecule" clearly refer to the molecule of the acidic substance; i.e. the DNA polymerase is trapped, thus inhibited, by the acidic substance. Furthermore, in light of this passage, the phrase "efficiently allows to exhibit the DNA polymerase activity or to hold the enzyme" (column 13, lines 14-18) is reasonably interpreted as describing a reversible inhibition of the polymerase, where "allows to exhibit DNA polymerase activity" describes a state where the polymerase is not inhibited, and "hold the enzyme" describes a state where the polymerase is inhibited.

In section A(ii) beginning on page 11 of the response, Applicant argues that Asada's teaching to modify MW (molecular weight) does not constitute a teaching to optimize molar ratios. Applicant agues two points on this issue, the first being the argument that Asada teaches "enhancing" rather than "inhibiting", which argument is not persuasive for the reasons discussed above. The second argument (middle paragraph, page 12 of the response), is that, while Asada discusses modifying molecular weight of the acidic substance, he "says nothing about varying its *molar concentration* relative to that of the polymerase" (emphasis in original). The rejection pointed out Asada's teaching to optimize the molecular weight of the acidic substance to meet the limitations of claims 23-25, which have to do with molecular weight. However, the rejection also pointed out Asada's teaching to optimize the *amount* of the acidic substance (see discussion of claims 30-31, page 9 of Office action mailed 01/07/2009 and see discussion of claims 30, 31, 57 and 58 above; see also column 10, lines 25-35 of the Uemori patent). In varying the amount of the acidic substance, one would inherently

vary the molar concentration of the acidic substance. Since Asada taught the purpose of the acidic substance was to trap excess polymerase (as discussed above), and since Asada also taught optimizing the amount of the acidic substance used, one of skill in the art was instructed by Asada to optimize the amount (hence the molar concentration) of acidic substance relative to the amount (hence molar concentration) of polymerase to achieve the reversible inhibition (trapping) of the polymerase by the acidic substance.

In section B of the response, beginning on page 13, Applicant further argues that Asada and Qiagen teach away from providing the polyanions (acidic substance) with the polymerase in the absence of template and primers. The rationale underlying this argument, however, is the same argument that Applicant makes regarding the interpretation of the purpose of Asada's acidic substance. As discussed above, Applicant's interpretation is inconsistent with Asada's teachings (especially the teaching of trapping excess DNA polymerase with the acidic substance). For this reason alone, Applicant's arguments regarding a "teaching away" are not persuasive. Moreover, regardless of whether one views Asada's acidic substance as a "reversible inhibitor" or a "PCR enhancer" or both, there is nothing in either Asada or Qiagen that teaches away from combining the polymerase and the acidic substance into a single reagent in a kit. Applicant argues on page 14 of the response: "As Asada touts the polymerization-enhancing function of its acidic substances and Qiagen contrarily teaches inhibiting the polymerization activity of a stored polymerase, the Office's proposed combination would be contrary to the express and intended purpose of Asada's acidic substances, one the one hand, and Qiagen's inhibited polymerase, one the other." As discussed above,

Asada teaches the acidic substances enhance a PCR reaction by trapping excess DNA polymerase (hence, acting as a reversible inhibitor). Furthermore, the rejection does not purport to combine the polymerase taught by Qiagen with the acidic substance taught by Asada. Rather, the rejection merely relies on Qiagen as providing a motivation to store the polymerase and acidic substance in the absence of primers and template nucleic acids.

For the reasons discussed above, Applicant's arguments are found unpersuasive and the rejections are maintained.

Claims 35 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Asada et al (WO 00/14218, the March 16, 2000 publication of international application PCT/JP99/04815) as evidenced by Uemori et al (USPN 6,673,578) and in view of Qiagen News (Issue No. 1, 1999, cover and pages 13-14) as applied to claims 22-34, 43-47, 49-61 and 63-65 above, and further in view of Tonoike et al (US 6,472,187). As the Asada reference was published in Japanese, USPN 6,673,578, which resulted from the national phase entry of PCT/JP99/04815 under 35 U.S.C. 371, will be used as an English translation, and all teachings will be pointed out with reference to the '578 patent.

The teachings of Asada and Qiagen News have been discussed. These references do not teach the reverse transcriptases recited in claims 35 and 62.

Tonoike teaches amplification of RNA using AMV reverse transcriptase (column 5, line 45). The reverse transcriptase reaction was performed at 55°C (column 6, lines

50-55). This, together with the fact that AMV is specifically recited in claims 35 and 62, evidences that AMV RT is "thermostable". The reaction was conducted in the presence of heparin (column 6, line 45). In fact, Tonoike expressly teaches to use sulfated polysaccharides such as heparin, heparan sulfate, chondroitin sulfate, fucoidan and dextran sulfate (column 4, lines 45-50).

It would have been *prima facie* obvious to one of ordinary skill in the art to modify the solution suggested by the combined teachings of Asada and Qiagen News to include AMV reverse transcriptase in order to allow for RNA amplification as disclosed by Tonoike, since both the PCR taught by Asada, and the reverse transcription and PCR taught by Tonoike, were expressly recommended to be carried out in the presence of the specific polyanionic substances recited in Applicant's claims. One would have been motivated to arrive at such a "stock solution", since Asada already suggested combining "some of the components" and since the Qiagen News article teaches the advantages of easy handling, less pipetting, and reduced possibility of errors and contamination.

Response to Arguments

Applicant's arguments filed 05/07/2009 have been fully considered but they are not persuasive. Applicant relies on the same arguments already addressed above, which, for the reasons discussed, are not persuasive.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 50-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 50-53, 57-59 and 63 depend from claim 51, and claim 51 depends from itself. For purposes of further examination, it will be assumed that all claims recited as depending from claim 51 should depend from claim 49.

Similarly, claim 54 depends from claim 55, which depends from claim 56, which depends from claim 57, which depends from claim 51. It will be assumed that claim 54 depends from claim 53, claim 55 depends from claim 54, and claim 56 depends from claim 55.

Similarly, claim 60 depends from claim 61, which depends from claim 62, which depends from claim 61. It will be assumed that claims 60-62 should each depend from claim 49.

Finally, claims 64 and 65 each depend from claim 65. It will be assumed that claims 64 and 65 each depend from claim 63.

These assumptions are made in a good faith effort by the examiner to construe the claims. Any amendments by Applicant in an after-final amendment to obviate this

rejection may be denied entry if these assumptions are no longer valid and would result in further search and consideration beyond a mere cursory review.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
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